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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 11

Application Number: 09/676,783
Filing Date: October 02, 2000
Appellant(s): MCBRIDE ET AL.

Stephen B. Maebius
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/8/03.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

de Jong et al, "Comparison of 111 In-labelled somatostatin Analogues for Scintigraphy and Radionuclide Therapy", Cancer Research vol. 58, (February, 1998), pp. 437-441.

Lewis et al, "Comparison of Four 64cu-Labeled Somatostatin Analogues in Vitro and in a Tumor-Bearing Rat Model: Evaluation of New Derivatives for Positron Emission Tomography Imaging and Targeted Radiotherapy", J. Med. Chem. vol. 42, (1999), pp. 1341-1347.

Lewis et al., "Radiotherapy and Dosimetry of 64 Cu-TETA-Tyr3-octreotate in a Somatostatin Receptor-positive, Tumor-bearing Rat Model", Clinical Cancer Research, vol. 5, (November, 1999) pp. 3608-3616.

Bugaj et al, "Radiotherapeutic efficacy of 153Sm-CMDTPA-Tyr3-octreotate in a tumor-bearing rats", Nucleic Med. Biol. vol. 28, (2001) pp. 327-334.

Paganelli et al, "Receptor-mediated Radionuclide Therapy with 90Y-DOTA-D-Phel-Tyr3-octreotide: Preliminary Report in Cancer Patients", Cancer Biother. Radiopharm. vol. 14, no. 6, (1999), pp. 477-483.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 24-40 and 42-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons advanced in the last Office action.

The specification fails to provide an adequate written description of a method of treating a tumor in human patients by administering a radiolabeled peptide or polypeptide to said human patients. There is not enough description in the specification as to the different kind of tumor(s), peptides, modes of administration, dosage and test procedures or steps in specific terms as to the treatment method. The specification describes in general an assay method as to the supposed binding effect of the peptides LHRH or VIP analogues to breast cancer

cells. However, no results are provided for said binding method. It is not readily apparent how said assay method translates or correlates the binding effect to a treatment method, absent any experimental results. Furthermore, the assay method uses the peptides, LHRH or VIP analogues. Claim 24 does not recite a named peptide or any structure for the peptide or polypeptide attached to the specific radiolabel compound. Accordingly, the general statements and general assay method provided in the specification fail to comply with the requirement of the statute as to a full, clear and concise description of the claimed method.

(11) Response to Argument

[As a preliminary matter, the 112 issues on appeal is lack of written description. It is neither an enablement issue (Brief at page 3, paragraph VIII) nor a utility issue (page 4, footnote and page 9 of the Brief]

Appellants argue they were in possession of the claimed method of treating a tumor using the claimed radiolabeled peptides, as the specification describes methods of radiolabeling peptides and in vitro assay method. Appellants further argue that at the time the application was filed, the level of skill in the art to which the invention pertains was such that it is not necessary for Appellants to include much

more detail in the Specification, in addition to the radiolabeling and in vitro experiments described therein, to demonstrate that they were in possession of a method for treating a tumor using the claimed radiolabeled peptides. Appellants also argue that at the time the application was filed, it was known that many peptides closely related to those claimed in claim 24 could be used in radionuclide therapy to treat tumors. The Specification, therefore, is ***enabling*** for the treatment of tumors with the claimed radiolabeled peptides, as argued. Claim 24, and the claims which depend upon it, should not have been rejected under 35 U.S.C. 112, first paragraph for allegedly lacking enablement.

In response, as admitted by appellants the written description teaches a ***specific*** method of radiolabelling the peptide and a ***general*** in vitro assay method. It is not apparent from the ***general*** in vitro assay method, the specific qualifying feature, if any, of the binding effect that translates into a therapeutic effect, absent any experimental results. Furthermore, there is no indication in the general assay method that the peptide LHRH or VIP compound employed are the ones in claim 24. The claim (24) does not recite a named peptide or any structure for the peptide or polypeptide. The specification describes the radiolabeling method of the peptide in terms of

its amino acid sequence or structure. Rather, than in terms of the named peptide. It is not clear from the structurally radiolableled peptide the ones that are the analogues of the named peptides, LHRH or VIP.

If appellants choose to rely upon general knowledge in the art to complete their disclosure then, appellants must show that anyone skilled in the art would have actually possessed the knowledge or to point out precisely where in the prior art said specific description lies. It is noteworthy that none of the prior art submitted by appellants, as discussed, infra, uses the named peptide analogues of LHRH or VIP. Rather, all of the prior art describe a different peptide analog, somatostatin (SMS). Generalized language or statement in the specification may not suffice if it does not convey the detailed identity of the invention. See University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003).

Appellants argue that the guidelines in Section 2163 themselves provide that "generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement.

In reply, at the time of appellants' invention, the field of chemistry, i.e., peptides is such that little prediction is possible. And its applicability, specifically to tumor treatment has been highly speculative or still not fully elucidated. The instant disclosure at page 2, line 27 u p to page 6, line 6 appears to support such. The disclosure recites "……[This] method further suffers from the problem that direct binding of the metal to an amino acid side chain can greatly influence the peptide conformation, thereby deleteriously altering the receptor binding properties of the compound……" Furthermore, as is well known in the art, peptides by its very nature readily undergo enzyme degradation, *in vivo*, as will be discerned from the prior art discussed, *infra*.

Appellants argue that information, which is well known in the art, need not be described in detail in the Specification. [Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986)].

As stated above, if an appellant choose to rely upon what is well known in the art to complete his disclosure, appellant must point out precisely where in the prior art said specific description lies. The generalized statement made in the specification does not suffice if it does not convey the detailed identity of the claimed invention. See University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003).

In support of Appellants' position, Appellants submitted journal articles that illustrated the level of skill in the art to which the invention pertains. Appellants argue that these articles demonstrated that, at the time the application was filed, it was known that peptides related to those claimed in the present application where promising in vitro candidates for the treatment of certain tumors. It is further argued that articles demonstrated that the in vitro results could be extrapolated to the use of such peptides in radionuclide therapy to treat certain tumors in vivo.

In reply, as admitted by applicants above, the references provide simply ***promising*** in vitro candidates for the treatment of ***certain*** (not any or all types, as claimed) of tumors using specific peptides.

Appellants argue that de Jong et al demonstrated that In-labeled **somatostatin analogs** showed high and specific binding in vitro to somatostatin receptors in mouse pituitary tumor cell membranes. De Jong et al, is argued to also show that all of the compounds that were evaluated, namely, the octreotides, showed specific internalization in rat pancreatic tumor cells. In addition, de Jong et al showed that these results translated to in vivo models. For example, biodistribution studies showed that radioactivity in the octreotide-binding, receptor expressing tissues and tumor-to-blood ratios were significantly higher when one octreotide is used relative to the other octreotides. Finally, it is argued that de Jong et al characterize radiolabeled (DTPA, Tyr3] octreotide, and especially (DTPA, Tyr3]octreotate and their DOTA-coupled counterparts as "most promising for scintigraphy and radionuclide therapy of (somatostatin) receptor-positive tumors in humans".

In response, de Jong, as appellants recognized, describes a specific method showing binding effect or biodistribution of a specific peptide, the somatostatin (SMS) analogs, octreotides, to tumor that specifically expresses said SMS. De Jong does not describe a general assay binding effect for any type of peptide that binds to any tumor expressing receptors. De Jong further

demonstrates that there is no a priori predicting the biodistribution of even related peptides in tumor cells. The concluding remarks state that the studies are not categorical.

Appellants argue that Lewis et al (EXIBIT B) illustrates in their studies, the structure activity relationship of various somatostatin analogs related to those described by de Jong et al (supra). Lewis et al compared the in vitro binding, in vitro tumor cell uptake, and in vivo distribution of radiolabel octreotide.

Lewis et al (Exhibit C) is argued to mention a previous study, which showed that [Cu-TETA] octreotide significantly exhibited (inhibited) the growth of somatostatin receptor-positive pancreatic tumors in Lewis rats. In the study, Lewis et al is argued to have found that a single dose of [Cu-TETA, Tyr3] octreotate was shown to be more effective in reducing tumor burden than the same dose of [Cu-TETA]octreotide. Lewis et al. also found that in multiple dose experiments, complete regression of tumors was observed for all rats treated with 3 x 20 mCi of [64Cu-TETA,Tyr3]octreotate; with no palpable tumors for approximately 10 days.

In response, each of the Lewis references, relate to studies on the structure activity relationship (SAR) of the compounds, octreotide analogs and its biodistribution in cells.

The studies are done to determine the compounds that would be considered as candidate agents that hold promise for therapy. Each of the studies concludes with the findings that greater tumor retention of one octreotide justifies the ***selection*** of this agent for ***future*** PET imaging and targeted **radiotherapy** ***studies***.

Appellants argue that Bugaj, using animal models, evaluated the radiotherapeutic efficacy of the radiolabel somatostatin analog octreotate, a compound related to the radiolabel peptides claimed in the present invention. Bugaj et al. focused on the beta- emitting nuclide chelated to the somatostatin analog, octreotate. Bugaj found that suppression of tumor growth rate was observed in all animals treated with octreotate compared to untreated controls. On page 332, column 2, of the Bugaj et al. article, it is mentioned that additional studies are necessary to determine whether the high pancreatic uptake observed in rats will also be found in humans. The results with other octreotate derivatives in primates, where no apparent pancreas uptake is observed in scintigraphs, suggest that this will not be the case. Appellants note, and the skilled artisan will recognize, that tumors in locations other than the pancreas may be treated using the compound reported by Bugaj et al notwithstanding Bugaj

et al's comments vis-à-vis testing of the reported compounds in primates.

In reply, if Bugaj already failed to demonstrate the efficacy of a specific octreotide analog as detailed in the methods, then what direction will one has to follow to successfully locate the tumors in other locations?

Appellants argue that when the instant application was filed, Paganelli et al had already demonstrated that a compound related to the radiolabel peptides claimed in the present invention, could be used to treat tumors in humans. Paganelli et al reports the dosage, safety profile and therapeutic efficacy of octreotide (DOTATOC) when patients with cancers expressing somatostatin receptors are treated with this compound. Paganelli et al also showed that out of 5 patients that were treated, complete and partial tumor mass reduction was measured in 25% of patients, along with 55% showing stable disease and 20% showing progressive disease. Paganelli et al is congruent with the notion that compounds such as those claimed in the present invention can be used to treat tumors in humans.

In reply, Paganelli article published after three (3) years from the time of filing. In the study Paganelli discover that after numerous experiments on octreotide peptide analogs, (not LHRH or VIP), its tumor efficacy can hardly be considered

statistically significant. Out of the only 5 patients treated, more than half showed no improvement and in one, the tumor is progressive. Like Lewis the study concludes "….the results of the **pilot** therapeutic study confirmed the **possibility** of delivering high radiation doses to the tumor using DOTATOC. **Promising** methods of reducing uptake in some organs (specifically kidneys) are **under study**……"

Appellants argue that Kwekkeboom demonstrated that SMS analogs were effective in treating tumors in animal models. For example, when the somatostatin analog was labelled with the beta- and gamma-emitting radionuclide, it had a favorable impact on tumor regression and animal survival in a rat model.

In response, the Kwekkeboom' studies came out five (5) years after the filing date. It reached the conclusion that the maximum dosage for smaller tumors has not been studied yet, since smaller tumors from which much of the radiation dose will be lost to the surrounding tissues.

Accordingly, only by painstaking experiments can one determine if a peptide has a therapeutic efficacy, especially against a disease as complex and not fully elucidated as tumors. As shown by the prior art above, numerous experimental studies have been undertaken and yet to be undertaken to find if a

single peptide as the SMS analog, has the sought-after therapeutic efficacy.

To allow appellants to dominate a highly unpredictable and not fully elucidated field based on the expediency of the prophetic, generalized statement or meaningless conclusion in the specification will not promote science as intended by the law. It will bar one who has actually worked and discovered the details of the treatment method. The law is clear in its requirement that the specification shall contain a written description of the invention in full, clear, concise and exact terms at the time of filing.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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